

“measuring the intensities of the mass spectrum of said first sample”, the Examiner comments that “it is obvious that they can do such.” The Examiner then states that because Kirchner et al teach that “by scanning rf voltages to the quadrupole filter, a mass spectrum can be generated to show the signal intensity versus m/z ratio.” Armed with that observation, the Examiner concludes that “it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure intensities of a first sample because this will increase the efficiency of the detection and subsequent analyzing process.” The Applicant respectfully disagrees.

In the first instance, the Applicant is uncertain what the Examiner meant by the term “efficiency”, as the present invention is not directed towards increasing “efficiency” of a mass spectrometer *per se*; but is rather directed towards increasing the dynamic range of the instrument. Indeed, using at least one sense of the word, the present invention renders a mass spectrometer less “efficient”, as the time required for analyzing any particular sample using the present method is increased. However, the small penalty in the time required to make a measurement is dwarfed by the gains in the sensitivity of the instrument, and the new-found ability to accurately detect and measure ions that may constitute an exceedingly small portion of a given sample. It is these benefits, which effectively increase the dynamic range of the mass spectrometer, that are the paramount focus of the present invention.

Importantly, it is not simply the act of “measur(ing) the intensities of the first sample” that leads to this increase in the dynamic range. The simple act of measuring intensities does nothing to change the physical operation, and thus the dynamic range, of the instrument. Rather, it is the use of the information gained in the measurement and subsequent modification of the rf voltages to remove a specific subset of the ions that enhances the instrument’s dynamic range. These steps are claimed by the Applicant in claims 1 and 8, steps c and e, (c. “identifying undesired ions within said first sample for ejection”; e. “applying the appropriate rf voltages to the quadrupole ion filter to eject the undesired ions”) and in all remaining claims by virtue of dependency. Notably, neither Schwarz nor Kirchner remotely teach or suggest either of these steps.

The Applicant will allow that prior to the present invention, those skilled in the art

mass spectrometry routinely scanned ion samples and measured the m/z ratio of those ions using mass spectrometers. What the Applicant does not concede, and what is not shown by either Schwarz et al., Kirchner et al. or the Examiner, is the use of the information gleaned from the measurement of an m/z ratio of a first scan to identify specific ions for ejection in a second scan, (or in successive scans) thereby allowing the instrument to “focus in” on specific ions of interest identified within the sample. Indeed, with respect to Kirchner, the Examiner has merely asserted that Kirchner recites the basic function of a mass spectrometer, to provide a spectrum of mass to charge, citing column 1, lines 41-54. What Kirchner does not teach or describe is the use of information gleaned from the mass spectrum to make adjustments in the operation of the instrument to increase its dynamic range. Notably, the Examiner has not asserted as such. Thus, with respect to forming a prima facie case of obviousness, Kirchner’s teaching identified by the Examiner adds nothing.

The Applicant identified this as the primary point of novelty of the present invention at page 3, columns 16-23 of the specification where the Applicant stated:

The present invention thus increases the dynamic range of a mass spectrometer by utilizing a quadrupole ion filter as a device to selectively remove one or more undesired ions (peaks), thereby allowing the accumulation and subsequent detection of desired ions in a mass analyzer, such as an ion trap operated as a mass analyzer, adjunct to the ion filter. Typically, but not meant to be limiting, the desired ions are those that are present at relatively low concentrations, while the undesired ions are those that are present at relatively high concentrations. Accordingly, the present invention finds particular utility in instruments where ion capacity is constrained, such as mass spectrometers which utilize ion trapping in their analysis and detection schemes.

The Applicant vigorously contests the Examiner’s assertion that such would be obvious to one of ordinary skill in the art at the time the invention was made. Indeed, a plain reading of Schwartz et al. and Kirchner et al., combined with the superior performance detailed in the examples of the present invention contained within the

specification, clearly indicates that such was not obvious.

Notably, Schwartz et al. was concerned with the same goals addressed by the present invention. At column 5, lines 27-30, Schwartz et al. state that “the improved performance (of the mass analyzing system) includes *increased dynamic range*, increased sensitivity, improved lower detection limit (sic), and reduction of space charge effects.” However, Schwartz et al. delineates the specific cause of the problems differently than the present invention. At column 4, lines 14-20, Schwartz et al. states the cause of the problem thusly:

When operating a mass spectrometer, the amount of ions entering the ion trap for analysis varies. In the prior art the ionization times have remained relatively constant. Thus, when the amount of ions exceeds a certain threshold level, sample saturation and space charge effects may result in the loss of mass resolution and sensitivity and errors in mass assignment.

Just as with the present invention, Schwartz et al. recognized that too many ions in the trap cause degradation in the sensitivity. However, rather than removing a subset of these ions (as practiced by the present invention) Schwartz et al. opt for a strategy whereby the total ion current is gated, to prevent excess ions from entering the trap. As described by Schwartz et al., this is accomplished by “an ion source from which ions are gated into a mass spectrometer; with a feedback feature which controls the number of sample ions gated into the mass spectrometer; thus one measurement of the total ion content in the mass spectrometer determines the gate time for the next ion introduction step.” (column 5, lines 30-36). As described by Schwarz et al., “this minimizes the saturation and space charge in the mass spectrometer.”

Note that neither Kirchner et al. or Schwatz et al. do ANYTHING to discriminate between “desired” ions and “undesired” ions. Under the Schwartz et al. scheme, both types of ions continue to be introduced into the mass spectrometer and collected in the trap in the exact same proportions, albeit in smaller total quantities due to the gating. Schwartz et al. describe this in even greater detail in the paragraphs beginning at column

9, line 61 through column 10, line 41 which read as follows:

More specifically, a preferred embodiment of the invention is as follows. Based on a combination of voltages applied by the programmable lens voltage supplies 55 and 57 and fast switching programmable lens voltage supply 56 to the focusing lens 51, 53, and 52, respectively, an estimated number of sample ions are gated from the continuous ion source 156 into the mass spectrometer 1 substantially in a direction indicated by arrow 17 through entrance 18 on end electrode 4. This number of ions may be gated by turning "on" (i.e., changing the voltage) the focusing lens 52 for a specified preselected time. A typical initial gate time would be 100 microseconds. A different number of sample ions may be gated into the mass spectrometer by using a different gate time.

Since the mass spectrometer has already established and maintained a substantially quadrupole field within its trap region 2, most sample ions entering the mass spectrometer are trapped and behave as predicted according to well-known principles in the art. As sample ions are ejected out of the mass spectrometer 1 through perforation 25 during a pre-scan, the total ion content information is determined by the instrument control and data acquisition processor 91. Based on an algorithm stored in a computer 150, a new gate time is calculated to substantially optimize the number of sample ions gated into the mass spectrometer during the next gate sequence.

In the next gate sequence, the instrument control and data acquisition processor 91 sends control signals on bus 130 to the fast switching programmable lens voltage supply 56. The control signals are used to control the length of the next ion gating time and hence, the number of sample ions. The fast switching programmable lens voltage supply 56 applies a voltage to focusing lens 52 to set up a differential potential across the focusing lens system and "open" the lens for an adjusted gate time. After the sample ions are gated into the mass spectrometer for a certain gate time, the programmable lens voltage supply 56 "closes" the lens by either turning

off or applying a different voltage to stop the transfer of sample ions from the continuous ion source 156 into the mass spectrometer 1. After mass analysis, a new total ion content information is obtained and, as before, the information is fed back into the instrument control and data acquisition processor 91. The computer 150 uses this data to set up a new gate time for the next gate sequence. The above sequence is repeated until the sample molecules of interest are depleted in the continuous ion source.

Note that although the ion source 156 may be continuous, that is, ions may be continuously formed in the ion source, the mass analysis step of the mass spectrometer is not continuous. Mass analysis or scanning occurs only after a set of sample ions, based on a designated gate time, are gated into the mass spectrometer.

Again, note that while Schwartz et al. do limit the ion current entering the trap at any one time, they do NOTHING to discriminate between the kinds of ions which are accumulating in the trap. In contradistinction, the present invention relies on precisely such discrimination to selectively remove unwanted ions (and their associated space charge effects) thereby allowing longer gating times, and larger volumes of the ions of interest to accumulate. This is described by the Applicant at the paragraph bridging pages 3 and 4 of the specification, which reads as follows:

first pass(ing) a sample of ions through the mass spectrometer having a quadrupole ion filter, whereupon the intensities of the mass spectrum of the sample are measured. From the mass spectrum, ions within this sample are then identified for subsequent ejection. Typically, the ions identified for subsequent ejection will be the most highly abundant species, as the ejection of these species produces the most additional "room" for further accumulation in the ion trap. However, it may not always be the case that ions are selected for ejection based purely on their abundance. In certain applications, ions are selected simply because they are not of interest to the desired analysis, even though they are not

the most abundant. The present invention should thus be broadly construed to include any application where ions are selectively ejected using rf excitation to make room for further accumulation.

Thus, the present invention differs significantly in approach to the Schwartz et al. method. Further, when compared to one and another, the method of the present invention clearly achieves significant improvements in dynamic range over and above the Schwartz et al. method. The present invention describes the improvements in the paragraphs beginning at page 8, line 6 and ending at page 18, line 14. Notably, the method of the present invention was compared directly to a method directly analogous to the Schwartz et al. method. At page 16, lines 2 through 5, the Applicant described the experiments thusly:

The non-selective accumulation mass spectra were obtained using a 0.5 s trapping in the accumulation quadrupole, while the data-dependent selective ejection of the most abundant ion species in the fly-through mode in the selection quadrupole was followed by a longer 1 s external accumulation period.”

In other words, two experiments were run. In one experiment, the trapping time was set to 0.5 seconds in a manner analogous to Schwartz et al. In the second experiment, a longer, 1 second accumulation time was attainable since unwanted ions identified in a first scan were being eliminated. The result of this strategy is given at page 17, line 28 through page 18 line 3, which states:

“It was found that the number of peptides detected with the alternating sequences (30,771 unique mass classes were identified with the overlap subtracted) was greater by about 35% than that acquired using the non-selective ion accumulation (where 22,664 unique mass classes were identified). The same methodology was subsequently applied with data-dependent selective ion ejection of the two and three most abundant ion species. A 40% increase in the number of unique mass classes was achieved when combining the non-selective ion accumulation with data-dependent selective ion ejection of the three most abundant ion species.”

In other words, the method of the present invention produced an increased dynamic range that allowed the identification of 35-40% more mass classes when compared with the Schwartz et al. method. Thus, Schwartz et al. and Kirchner et al. cannot possibly provide a basis for a prima facie case of obviousness under 35 USC 103(a) because neither Kirchner et al. nor Schwartz et al. teach or suggest the steps of “identifying undesired ions within said first sample for ejection” or “applying the appropriate rf voltages to the quadrupole ion filter to eject the undesired ions” as required by steps c and e of independent claims 1 and 8, and all remaining claims by virtue of dependency. Such a teaching or suggestion is required for the Examiner to set forth a prima facie case of obviousness. As stated by the Board of Patent Appeals and Interferences, “To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Given the demonstrated improvement in the dynamic range of the mass spectrometer when compared to the method taught by Schwartz et al., no “convincing line of reasoning” is possible. As stated by the Federal Circuit, “when differences that may appear technologically minor nonetheless have a practical impact, particularly in a crowded field, the decision-maker must consider the obviousness of the new structure in this light. Such objective indicia as commercial success, or filling an existing need, illuminate the technological and commercial environment of the inventor, and aid in understanding the state of the art at the time the invention was made.” *Continental Can co. USA v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ 2d 1746, 1752 (Fed. Cir. 1991).

Plainly, Schwartz et al. were attempting to achieve precisely the same increase in dynamic range as is achieved by the present invention. Equally plain is the fact that the present invention achieved a far greater increase than is possible using the Schwartz et al. method alone. Accordingly, even if the Examiner maintains the conclusion that the combination claimed by the Applicant’s claims 1 and 8 is obvious, the improved dynamic

range demonstrated by the Applicant would render the claimed invention unobvious.

Again, as stated by the Federal Circuit:

Evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision-maker remains in doubt after reviewing the art. *Stratoflex, Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1538-40, 218 USPQ 871, 879 (Fed. Cir. 1983).

Accordingly, the Applicant respectfully requests that the Examiner remove his rejection of claims 1, 3, 5 and 7 based on the combination of Schwartz et al. and Kirchner et al.

The Examiner has rejected claims 2, 4, 6, 8, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al (USP 5,572,022) in view of Kirchner et al. (USP 5,464,975), and further in view of Syage et al. (USP 6,326,615). Regarding claims 2 and 8, the Examiner notes that Syage et al. teaches the interposition of an ion trap in between the quadrupole and the mass analyzer. The Examiner then asserts that the use of a filter is “known in the art.” However, the Examiner does not contend, nor does Syage et al. teach, the use of the filter to selectively remove ions identified as undesired in a first sample.

As with the analysis of Schwartz et al. and Kirchner et al. above, this limitation is fundamental to the present invention. With respect to the limitations of “identifying undesired ions within said first sample for ejection” and “applying the appropriate rf voltages to the quadrupole ion filter to eject the undesired ions” contained in claim 8, and claim 2 by virtue of dependency, Syage et al. does not enhance the teachings of Schwartz et al. and Kirchner et al. at all. Thus, any combination of Schwartz et al., Kirchner et al., and Syage et al. is insufficient to form the basis of a prima facie case of obviousness.

Regarding claims 4, 6, 9, 10 and 11, the Examiner returns to the teaching of Schwartz et al. and asserts that “it is known in the art of sample detection that numerous samples can be detected in a similar fashion, and that rf voltages can be generated by quadrupolar excitation to electrodes of an ion trap, quadrupole filter, or other suitable device as taught by Schwartz et al.” While the Examiner’s observation is at least relevant to the additional limitations of claims 4, 6, 9 and 10, it does not address the further limitation contained in each of these claims by virtue of their dependency on claims 1 and 8 that the identification of undesired ions forms the basis for the selection of the specific rf voltages that are applied, regardless of the device used. Accordingly, Schwartz still fails to provide the basis for a prima facie case of obviousness under 25 USC 103(a) with respect to claims 4, 6, 9, and 10.

With respect to claim 11, the Examiner has not even addressed the limitation that “steps a-h are repeated to detect further undesired ions for ejection.” This omission is telling, since this particular dependent claim isolates and amplifies the core novelty of the present invention. By repeatedly and successively selecting more and more undesired ions for removal over the course of several passes, the method of the present invention allows the operation of the instrument in a manner wherein the user is able to “hone in” on the desired ions by successively eliminating undesired ions that take up valuable space within the ion trap. In this manner the already remarkable enhancements to the mass spectrometer’s dynamic range are further enhanced, and the ability to accurately detect progressively smaller concentrations of desired ions within a given sample is created. Neither Schwartz et al, Kirchner et al., Syage et al., or the Examiner’s contentions about what is “known in the art” ever address this capability, or the steps taken to achieve this capability as they are set forth in the limitations of claims 1, 8, and 11. Accordingly, the Examiner’s failure to specifically address claim 11 can be interpreted as an admission that the Examiner realizes that none of the prior art teach or suggest these critical aspects of the method of the present invention.

The Applicant therefore respectfully requests that the Examiner remove his rejection of

claims 2, 4, 6, 8, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al (USP 5,572,022) in view of Kirchner et al. (USP 5,464,975), and further in view of Syage et al. (USP 6,326,615).

Closure

Applicant has made an earnest attempt to place the above referenced application in condition for allowance and action toward that end is respectfully requested. Should the Examiner have any further observations or comments, he is invited to contact the undersigned for resolution.

Respectfully submitted,

Douglas E. McKinley, Jr.

Reg. No. 40,280

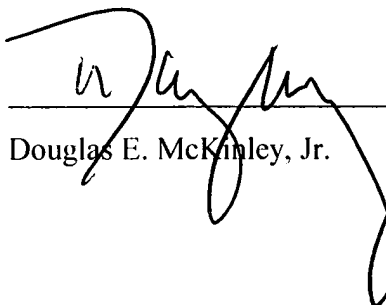
Douglas E. McKinley, Jr.

PO Box 202

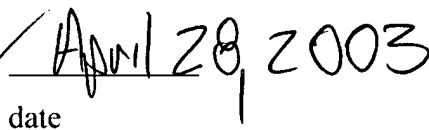
Richland, WA 99352

(509) 586-8931

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Douglas E. McKinley, Jr.



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